Claims

We Claim:

1. A solid support composition comprising:
   a) an acid forming cleavable linker; and
   b) a PNA dimer, comprising an N-terminal base labile protecting group, cleavably linked to the solid support through the cleavable linker, wherein the loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram.

2. The composition of claim 1, wherein the solid support is a sterically hindered solid support.

3. The composition of claim 2, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

4. The composition of claim 1, wherein the solid support is selected from the group consisting of: PAL-PEG-PS™, NovaSyn TGA and Wang Resin.

5. The composition of claim 1 or 2, wherein the PNA dimer is linked to the cleavable linker by an ester bond.

6. The composition of claim 1 or 2, wherein the PNA dimer is formed from Fmoc(Bhoc) monomers.

7. The composition of claim 1 or 2, wherein the loading of the PNA dimer on the solid support is in the range from about 0.1 mmol per gram to about 1 mmol per gram.

8. The composition of claim 1 or 2, wherein the loading of the PNA dimer on the solid support is in the range from about 0.12 mmol per gram to about 0.35 mmol per gram.

9. The composition of claim 1 or 2 wherein the solid support is an array comprising two or more different support bound PNA dimers.

10. A library comprising at least two solid supports wherein said at least two solid supports each comprise:
    a) an acid forming cleavable linker; and
    b) a PNA dimer that: (i) is cleavably linked to the acid forming cleavable linker; and (ii) differs in nucleobase sequence from the PNA dimer that is linked to any of the other of the at least two solid supports of the library.

11. The library of claim 10, wherein the library comprises at least sixteen solid supports, each support comprising a PNA dimer chosen from a set of at least sixteen possible PNA dimers wherein each PNA dimer of the set differs from all of the other PNA dimers of the set by at least one of at least four different nucleobases.

12. The library of claim 11, wherein each of the at least four different nucleobases is selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

13. The library of claim 10, wherein the solid support is a sterically hindered solid support.

14. The library of claim 13, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

15. The library of claim 10, wherein the solid support is selected from the group consisting of: PAL-PEG-PS, NovaSyn TGA and Wang Resin.

16. The library of claim 10 or 13, wherein the PNA dimer is linked to the cleavable linker by an ester bond.

17. The library of claim 16, wherein the C-terminal subunit of the PNA dimer is linked to the cleavable linker.

18. The library of claim 13, wherein the PNA dimer is formed from Fmoc(Bhoc) protected PNA monomers.

19. The library of claim 10 or 13, wherein the PNA dimer is formed from t-boc/Z protected PNA monomers.

20. The library of claim 10 or 13, wherein the PNA dimer is formed from Mmt/Bhoc protected PNA monomers.

21. The library of claim 10 or 13, wherein the PNA dimer is formed from both Mmt/Bhoc protected PNA monomers and Fmoc(Bhoc)protected PNA monomers.

22. The library of claim 10 or 13, wherein the loading of the PNA dimer on at least one solid support of the library is greater than or equal to 0.08 mmol per gram.

23. The library of claim 10 or 13, wherein the loading of the PNA dimer on at least one half of the solid supports of the library is greater than or equal to 0.08 mmol per gram.

24. The library of claim 10 or 13, wherein the loading of the PNA dimer on all of the solid supports of the library is greater than or equal to 0.08 mmol per gram.

25. The library of claim 24, wherein the loading of the PNA dimer on each solid support of the library is in the range from about 0.1 mmol per gram to about 1 mmol per gram.

26. The library of claim 24, wherein the loading of the PNA dimer on each solid support of the library is in the range from about 0.12 mmol per gram to about 0.35 mmol per gram.

27. The library of claim 10 or 13, wherein the library of supports is arranged to produce an array.

28. A method for forming a support bound PNA dimer, said method comprising:
    a) coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker wherein the PNA monomer comprises a N-terminal amine base labile protecting group;
    b) optionally washing the solid support to remove excess first PNA monomer;
    c) treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support bound first PNA monomer but that does not allow for more than 50 percent cyclization and elimination of the first PNA monomer from the support;
    d) washing the solid support to remove the deprotection reagent; and
    e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer as soon as is practical after performing steps (c) and (d).

29. The method of claim 28, wherein the first and second PNA monomers are Fmoc(Bhoc) PNA monomers comprising the same or a different nucleobase.

30. The method of claim 29, wherein the nucleobase of the first and second PNA monomer is independently selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

31. The method of claim 28, wherein the N-terminal base labile protecting group is Fmoc.

32. The method of claim 28, wherein the deprotection reagent is a solution containing from about 15 to about 25 percent (v/v) piperidine in an organic solvent.

33. The method of claim 32, wherein the deprotection reagent is 20 percent (v/v) piperidine in N,N'-dimethlyformamide (DMF).

34. The method of claim 28, wherein the deprotection reagent is a solution containing from about 0.2% to about 4% (v/v) DBU in NMP.

35. The method of claim 34, wherein the deprotection reagent is about 2% DBU in NMP.

36. The method of claim 28, wherein the sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

37. The method of claim 28, wherein the sterically hindered solid support is Trityl chloride (Trityl-Cl) resin.

38. The method of claim 28, wherein the final loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram.

39. The method of claim 28, wherein the final loading of the PNA dimer on the solid support is in the range from about 0.1 mmol per gram to about 1 mmol per gram.

40. The method of claim 28, wherein the final loading of the PNA dimer on the solid support is in the range from about 0.12 mmol per gram to about 0.35 mmol per gram.

41. A method for forming a support bound PNA dimer, said method comprising:
    a) coupling a first PNA monomer to solid support comprising an acid forming cleavable linker wherein the PNA monomer comprises an acid labile N-terminal protecting group;
    b) optionally washing the solid support to remove excess first PNA monomer;

c) treating the solid support with a deprotection reagent under acidic conditions that deprotect the acid labile N-terminal protecting group;

d) washing the solid support to remove the deprotection reagent; and

e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer,

wherein the final loading of the PNA dimer on the solid support is greater than or equal to 0.08 mmol per gram.

42. The method of claim 41, wherein the first and second PNA monomers are t-boc/Z protected PNA monomers comprising the same or a different nucleobase.

43. The method of claim 41, wherein the first and second PNA monomers are Mmt/Bhoc protected PNA monomers comprising the same or a different nucleobase.

44. The method of claim 41, wherein the first PNA monomer is an Mmt/Bhoc protected PNA monomer and the second PNA monomer is an Fmoc/Bhoc protected PNA monomer.

45. The method of claim 41, wherein the nucleobase of the first and second PNA monomer is independently selected from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

46. The method of claim 41, wherein the first PNA monomer is an Mmt/Bhoc protected PNA monomer and the deprotection reagent is a solution containing from about 1 to about 5 percent (v/v) dicloroacetic acid in an organic solvent.

47. The method of claim 46, wherein the deprotection reagent is about 2 percent dichloroacetic acid in dichloromethane (DCM).

48. The method of claim 41, wherein the solid support is a sterically hindered solid support is selected from the group consisting of: Trityl chloride resin (Trityl-Cl), 2-Chlorotrityl chloride resin, DHPP, MBHA, 4-methyltrityl chloride resin, 4-methoxytrityl chloride resin, Hydroxy-(2-chorophenyl)methyl-PS, Rink Acid Resin and NovaSyn TGT alcohol resin.

49. The method of claim 41, wherein the solid support is selected from the group consisting of: Fmoc-PAL-PEG-PS, NovaSyn TGA and Wang Resin.

50. The method of claim 41, wherein the final loading of the PNA dimer on the solid support is in the range from about 0.1 mmol per gram to about 1.2 mmol per gram.

51. The method of claim 41, wherein the final loading of the PNA dimer on the solid support is in the range from about 0.12 mmol per gram to about 0.35 mmol per gram.

52. A PNA C-terminal acid oligomer comprising a C-terminal PNA subunit and a fluorescent label or quencher.

53. The PNA oligomer of claim 52, wherein the fluorescent label is Dye 1 or Dye 2.

54. The PNA oligomer of claim 52, wherein the quencher moiety is dabcyl.

55. The PNA oligomer of claim 52, wherein the PNA oligomer is 10 or less PNA subunits in length.

56. The PNA oligomer of claim 52, wherein the PNA oligomer is from about 3 to about 8 subunits in length.

57. The PNA oligomer of claim 52, wherein the oligomer is from about 4 to about 6 subunits in length.

58. The PNA oligomer of claim 52, wherein the PNA oligomer is 4 subunits in length.

59. The PNA oligomer of claim 52, wherein the PNA oligomer is 5 subunits in length.

60. The PNA oligomer of claim 52, wherein the label is linked to the N-terminal subunit of the PNA oligomer.

61. The PNA oligomer of claim 52, wherein the label is linked to the N-terminal amine of the PNA oligomer.

62. The PNA oligomer of claim 52, wherein the nucleobases of the oligomer are selected from the group from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

63. A library of PNA C-terminal acid oligomers, each PNA oligomer of the library comprising:

a) a nucleobase sequence;

b) a C-terminal PNA subunit; and

c) a fluorescent label or quencher moiety;

wherein each PNA oligomer differs, either in label, nucleobase sequence, subunit length or polarity of nucleobase sequence, from each of the other PNA oligomers of the library.

64. The library of claim 63, wherein the nucleobases of each PNA oligomer are selected from the group from the group consisting of: adenine, cytosine, guanine, thymine, uracil, 5-propynyl-uracil, 2-thio-5-propynyl-uracil, 5-methylcytosine, pseudoisocytosine, 2-thiouracil and 2-thiothymine, 2-aminopurine, N9-(2-amino-6-chloropurine), N9-(2,6-diaminopurine), hypoxanthine, N9-(7-deaza-guanine), N9-(7-deaza-8-aza-guanine) and N8-(7-deaza-8-aza-adenine).

65. The library of claim 63, wherein the fluorescent label or quencher of each PNA oligomer is linked to the N-terminal subunit.

66. The library of claim 63, wherein the fluorescent label or quencher of each PNA oligomer is linked to the N-terminal amine.

67. The library of claim 63, wherein each PNA oligomer of the library comprises the same number of PNA subunits.

68. The library of claim 63, wherein at least one of the PNA oligomers of the library comprise a different number of PNA subunits as compared to at least one other PNA oligomer of the library.

69. The library of claim 63, wherein each PNA oligomer of the library comprises from about 3 to about 8 PNA subunits.

70. The library of claim 63, wherein each PNA oligomer of the library comprises from about 4 to about 6 PNA subunits.

71. The library of claim 63, wherein each PNA oligomer of the library comprises 4 PNA subunits.

72. The library of claim 63, wherein each PNA oligomer of the library comprises 5 PNA subunits.

73. The library of claim 63, wherein the library comprises at least two sets of PNA C-terminal acid oligomers wherein the PNA oligomers of each set differ from those of the other set primarily in the nature of a fluorescent label.

74. The library of claim 73, wherein the first set of PNA C-terminal acid oligomers is labeled with Dye1 and the second set of PNA C-terminal acid oligomers is labeled with Dye2.